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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,893	01/17/2001	Shih-Chieh Hung	11709-003001	6011

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/761,893	HUNG ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6,9-20,32 and 33* is/are pending in the application.

4a) Of the above claim(s) *12-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,9-11,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 10/11/2007, in which claims 1 and 33 were amended. Currently, claims 1, 4, 6, 9-20, 32 and 33 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group I without traverse in the reply filed on 9/4/2001.

Claims 12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/4/2001.

Currently, claims 1, 4, 6, 9-11, 32 and 33 are under consideration.

Response to Arguments - Claim Objections

The objection of claim 33 has been withdrawn in view of Applicant's amendment to the claim in the reply filed 10/11/2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6, 9, 11, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan et al (US Patent No. 5,811,094; see the entire reference) in view of Rieser et al (US Patent No. 6,242,247 B1, cited in a prior action; see the entire reference) and Burkitt et al (Wheater's Functional Histology (1993), page 60, cited in a prior action). This rejection was made in the Office action mailed 9/19/2007 and is reiterated below.

Caplan et al teach a method for recovering mesenchymal stem cells from human bone marrow aspirate from iliac crest, femora, tibiae, spine, rib or other medullary spaces, comprising the steps of (i) providing the bone marrow aspirate, which is a cell mixture comprising mesenchymal stem cells and other types of cells, (ii) seeding the cell mixture in a device comprising an upper plate comprising a Leukosorb™ filter, which contains pores through which other cells, such as fat cells and red blood cells, pass through, and which retains the mesenchymal stem cells, which adhere to the Leukosorb™ filter, and (iii) recovering the mesenchymal stem cells from the Leukosorb™ filter (upper plate) (e.g., column 45, line 41 to column 46, line 34). The specification does not explicitly define the term "culture device."

Given the broadest reasonable interpretation of the term, the device comprising the bone marrow aspirate or bone marrow culture of Caplan et al is a culture device. Caplan et al teach the further enrichment of mesenchymal stem cells from the cell population recovered from the Leukosorb™ filter specifically by passage over porous hydroxyapatite granules and by monoclonal antibody separation (e.g., column 46, lines 11-61). Further, Caplan et al teach that human mesenchymal stem cells isolated by their methods can be cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 1 g/L of glucose and supplemented with 10% fetal bovine serum to allow the mesenchymal stem cells to grow without differentiation and to allow the direct adherence of only the mesenchymal stem cells to the plastic or glass surface of the culture dish (e.g., column 8, line 20 to column 9, line 45). Further, Caplan et al teach that culturing in DMEM containing 1g/L glucose makes it possible to separate mesenchymal stem cells from other cells such as red and white blood cells, other differentiated mesenchymal stem cells, etc., which are present in bone marrow (e.g., column 8, lines 20-45). Caplan et al teach the removal of the non-adherent matter (i.e., medium and cells that are not adherent) from the culture dish (e.g., column 2, lines 3-19). Thus, Caplan et al generally teach that mesenchymal stem cells can be further enriched by passage over porous hydroxyapatite granules, by monoclonal antibody separation, and by selective adherence in DMEM with glucose and fetal bovine serum. Caplan et al teach that the mesenchymal stem cells can differentiate into bone, cartilage or adipose tissue (e.g., column 1, lines 40-52; column 47, lines 9-48).

Caplan et al do not specifically teach the method where the cells that pass through the pores of the top plate collect on a lower plate base. Caplan et al do not specifically teach culturing the mesenchymal stem cells on the top plate in 10% fetal bovine serum-supplemented

Dulbecco's modified Eagle's medium containing 1 g/L glucose and do not teach removing cells not adhered on the top plate by changing a culture medium.

Rieser et al teach a method comprising the steps of (i) providing bone marrow using a method known in the art, (ii) introducing the bone marrow comprising mesenchymal stem cells to a cell space (1), closing the cell space, and introducing it into the culture medium, which results in the introduction of mesenchymal stem cells above a bone substitute plate (7) (upper plate) and a bottom plate, which is the bottom of the culture dish (e.g., column 5, lines 15-36, column 6, line 56 to column 7, line 3; Figure 1). Rieser et al teach that the cells in the cell space settle on the bone substitute plate (7) due to the effects of gravity (e.g., column 7, lines 24-34). Once the cells have settled on the plate, they adhere and grow (e.g., column 7). Rieser et al teach the subsequent removal of cartilage formed from the cells introduced into the cell space (e.g., paragraph bridging columns 6-7). Rieser et al teach that the bone substitute plate (7) serves two functions: it is a permeable wall for the cell space (1), and it provides a substrate for the adherence of cells (e.g., column 7, lines 7-24). With respect to the porosity of the upper plate (7), Rieser et al teach pores of 1 to 20 μm are suitable, as well as pores between 20 and 50 μm (e.g., column 7, lines 34-54).

Burkitt et al teach that red blood cells are 6.7-7.7 μm in diameter and nucleated cells have a diameter greater than 7.7 μm (page 60).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of isolating mesenchymal stem cells of Caplan et al to include the introduction of the bone marrow aspirate into the cell space and culture dish taught by Rieser et al because Caplan et al teach it is within the ordinary skill in the art to use a filter to remove

red blood cells from bone marrow aspirate and Riser et al teach the use of a porous filter, where the pore diameter can be modified, in combination with the teachings of Burkitt et al, to allow red blood cells to pass through the pores while the nucleated cells remain on the filter. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Dulbecco's modified Eagle's medium containing 1 g/L glucose supplemented with 10% fetal bovine serum (DMEM-LG with 10% FBS), taught by Caplan et al, in the culture dish and cell space, because Rieser et al teach culturing the cells in the dish in the presence of medium. Moreover, it would have been obvious to change the medium to allow the continued growth of the cells in an undifferentiated state while removing other non-adherent, non-mesenchymal stem cells.

One would have been motivated to make such a modification in order to receive the expected benefit of eliminating the extra steps of washing the cells from the filter and performing subsequent purification steps as taught by Caplan et al. The use of the DMEM-LG with 10% FBS and media changes would result in an enriched population of cells. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Caplan et al (US Patent No. 5,811,094; see the entire reference) in view of Rieser et al (US Patent No. 6,242,247 B1, cited in a prior action; see the entire reference) and Burkitt et al (Wheater's Functional Histology (1993), page 60, cited in a prior action) as applied to claims 1, 4, 6, 9, 11, 32 and 33

above, and further in view of Pittenger et al (Science, Vol. 284, pages 143-147, 1999, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 9/19/2007 and is reiterated below.

The combined teachings of Caplan et al, Rieser et al, and Burkitt et al et al are described above and applied as before.

Caplan et al, Rieser et al, and Burkitt et al do not specifically teach that the mesenchymal stem cells are CD34-.

Pittenger et al teach the isolation of human mesenchymal cells from bone marrow taken from the iliac crest (e.g., page 143, right column). Pittenger et al teach that the mesenchymal stem cells are CD34- (e.g., paragraph bridging pages 143-144). The mesenchymal stem cells isolated by Pittenger et al are capable of differentiating to adipose, cartilage or bone tissue (e.g., Figure 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to specifically use a bone marrow aspirate from human iliac crest, because Caplan et al and Pittenger et al teach the use of bone marrow from iliac crest to isolate mesenchymal stem cells that are capable of differentiating to adipose, cartilage or bone tissue (e.g., Figure 2). It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute iliac crest bone marrow for any other type of bone marrow to achieve the predictable result of recovering CD34- mesenchymal stem cells that are also capable of differentiating to adipose, cartilage or bone tissue.

Response to Arguments - 35 USC § 103

The rejection of claims 1, 4, 6, 9 and 11 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Muschler et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/11/2007. Caplan et al do not teach the step of culturing on the Leukosorb™ filter, and Muschler et al do not teach culturing the progenitor cells in the disclosed device.

The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Muschler et al and further in view of Pittenger et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 10/11/2007. Caplan et al do not teach the step of culturing on the Leukosorb™ filter, and Muschler et al do not teach culturing the progenitor cells in the disclosed device. Pittenger et al do not remedy the deficiencies of Caplan et al or Muschler et al.

With respect to the rejection of claims 1, 4, 6, 9, 11, 32 and 33 under 35 U.S.C. 103(a) as being unpatentable over Caplan et al in view of Rieser et al, and Burkitt et al, Applicant's arguments filed 10/11/2007 have been fully considered but they are not persuasive.

At paragraph 3.1, the response notes that Caplan et al do not teach the step of culturing the cells on the porous filter. This deficiency is remedied by the teachings of Rieser et al. Rieser et al teach culturing the cells on the porous plate (e.g., column 6, lines 58-62). Further, the response asserts that Caplan et al teach away from the claimed invention, which uses the device to culture the cells. Specifically, the response asserts that the further elution prior to culturing, which is taught by Caplan et al, constitutes a teaching away. This is not found persuasive. Caplan et al teach the use of a Leukosorb™ filter to remove cells such as fat cells and red blood

cells from preparations of mesenchymal stem cells. The size of the pore of the filter allows this separation. Rieser et al teach a culture device that contains a porous plate. The pores of the plate in the culture device of Rieser et al will be capable of allowing the fat cells and red blood cells to pass through and thus serves a similar purpose as the Leukosorb™ filter as Caplan et al. Rieser et al teach that it is desirable to culture mesenchymal stem cells in the disclosed device (e.g., column 5, lines 15-25). The disclosure of Caplan et al does not serve to criticize, discredit, or otherwise discourage the use of a porous filter in a culture device and thus does not constitute a teaching away from the combination of references.

At paragraph 3.2, the response notes that Caplan et al do not specifically teach the culturing of the mesenchymal stem cells recovered from the Leukosorb™ filter in 10% fetal bovine serum-supplemented Dulbecco's modified Eagle's medium containing 1 g/L glucose. The response also notes that Caplan teaches further enrichment of the cells collected from the Leukosorb™ filter by passing the cells over a hydroxyapetite column and by using monoclonal antibody selection. This is not found persuasive. 35 U.S.C. 103 authorizes a rejection where, to meet the claim, it is necessary to modify a single reference. In the instant case, Caplan et al teach that culturing in 10% fetal bovine serum-supplemented Dulbecco's modified Eagle's medium containing 1 g/L glucose provides an enrichment of mesenchymal stem cells as a result of selective adherence. Caplan et al teach that in culturing in Dulbecco's Modified Eagle's Medium (DMEM) containing 1 g/L of glucose and supplemented with 10% fetal bovine serum allows the mesenchymal stem cells to grow without differentiation and allows the direct adherence of only the mesenchymal stem cells to the plastic or glass surface of the culture dish (e.g., column 8, line 20 to column 9, line 45). Thus, it would have been obvious to one of

ordinary skill in the art at the time the invention was made to substitute the hydroxyapetite column and monoclonal antibodies with the culturing step, in order to achieve the predictable result of producing an enriched population of mesenchymal stem cells.

At paragraph 4, the response discusses the Muschler reference. As stated above, the rejections based upon the Muschler reference have been withdrawn.

At paragraph 5.1, the response asserts that Rieser et al do not teach a method for recovering mesenchymal stem cells from human bone marrow aspirate or a cell mixture. These elements of the claimed invention are taught by Caplan et al. The limitations of the claimed invention are met by the combined teachings of Caplan et al and Rieser et al. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

At paragraph 5.2, the response asserts that the plate of Rieser et al functions differently than the claimed plate even though the pore sizes are similar. The response asserts that the plate of Rieser is for cell growth and is not a filter. This is not found persuasive, because the claims require the plate to be a filter and a substrate for culturing the cells. The structure taught by Rieser et al meets the structural and functional limitations of the claims in that it would allow the fat cells and red blood cells to pass through, while retaining mesenchymal stem cells for culturing. The response does not provide objective evidence demonstrating that the plate taught by Rieser et al is not capable of performing the claimed function. The response asserts that is would not have been obvious to introduce bone marrow into the cell space taught by Rieser et al.

This is not found persuasive, because Rieser et al teach the introduction of bone marrow and mesenchymal stem cells into the cell space (e.g., column 5, lines 15-25).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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